HAUTE AUTORITÉ DE SANTÉ

RECOMMEND
PUBLIC HEALTH STRATEGIES

GUIDELINE

RSV infection vaccination recommendation for pregnant women

Validated by the Board on 6 June 2024

Synopsis

Every year in France, almost 30% of infants under two years are affected by bronchiolitis (all viruses combined), and 2 to 3% of all infants under one year are reportedly hospitalised for severe bronchiolitis.

The seasonal epidemic generally starts mid-November, peaking in December and finishing once winter has come to an end. After COVID-19 prevention measures were lifted, the 2022-2023 season was characterised by a particularly early start, a prolonged duration and a high intensity, leading to extraordinary pressure on the paediatric and outpatient care system.

The Abrysvo vaccine developed by the firm Pfizer was granted a European marketing authorisation on 23 August 2023. It was granted an indication for passive protection against lower respiratory tract illness caused by respiratory syncytial virus (RSV) in infants from birth to 6 months of age following active maternal immunisation during pregnancy.

The French Ministry of Health (DGS) submitted a referral to the HAS on 4 May 2023 with a view to assessing the relevance of incorporating this new vaccine in the RSV infection prevention strategy.

The purpose of this report is to analyse all of the data available with a view to assessing the relevance of incorporating vaccination of pregnant women with the Abrysvo vaccine in the RSV infection prevention strategy for infants.

To this end, the HAS took into consideration:

– **The clinical expression of RSV infection in newborns and infants** ranging from a simple "cold" to bronchiolitis and pneumonia; cases of bronchiolitis being generally mild with spontaneous recovery occurring after 5 to 10 days;

– **The lack of long-term immunity resulting from natural RSV infection**;

– **The high circulation of RSV**: every year, bronchiolitis affects almost 30% of infants under 2 years, representing approximately 480,000 cases per year. Every year, 2 to 3% of infants under 1 year are reportedly hospitalised for more severe bronchiolitis. Deaths attributable to acute bronchiolitis are very rare (less than 1%). Bronchiolitis epidemics represent the leading cause of paediatric hospital admissions, disrupting the operation of emergency and paediatrics departments. In 2023-2024, RSV was involved in 73% cases of bronchiolitis admitted to intensive care (alone or coinfection), and was the only pathogen identified in 63% of cases admitted to intensive care (representing 381 and 328 cases, respectively). The cases were mostly under 6 months of age (79%), and 28% of cases had at least one identified comorbidity or were premature. No deaths among the cases were reported.

– **Epidemiological status:**
  - prior to the emergence of SARS-CoV-2: the epidemic usually commenced in mainland France mid-November, peaking in December and finishing at the end of January.
  - Since the emergence of COVID-19, bronchiolitis epidemics have been substantially disrupted. **The 2023-2024 seasonal epidemic** started mid-October, which was early

compared to pre-COVID-19 seasons, with the epidemic commencing 4 weeks earlier than the average over the 2010-2020 seasons, but 2 weeks later than the previous 2 seasons. Substantial differences in seasonality of bronchiolitis epidemics in overseas territories, in particular since the COVID-19 pandemic;

– **Medical RSV infection management** essentially based on supportive care and the lack of specific therapeutic option for this infection;

– **The implementation in September 2023 of a passive immunisation campaign with monoclonal antibodies** (nirsevimab, Beyfortus) organised by public authorities for all infants born from 6 February 2023 in Metropolitan France saw strong uptake among healthcare professionals and parents. Indeed, an IPSOS survey funded by Sanofi reports that 8 out of 10 parents agree to immunise their infants at the maternity hospital, and the first data collected by Sanofi in Spain (survey in Galicia) indicate passive immunisation coverage rates in excess of 80% in eligible populations.

– **The characteristics of the Abrysvo vaccine**, non-adjuvanted bivalent recombinant vaccine consisting of equal quantities of two stabilised F antigens, referenced 847A and 847B, representing RSV sub-groups A and B, respectively;

– **The efficacy data in respect of the Abrysvo vaccine** in 7128 newborn infants whose mothers were vaccinated during pregnancy, obtained from the MATISSE study, a Phase 3, multicentre, double-blind placebo-controlled trial randomised in two parallel arms, demonstrating that only one of the two primary endpoints of this study achieved a statistically significant superiority:
  - reduction in cases of medically attended RSV-associated lower respiratory tract infections (RSV-LRTI) (vaccine efficacy (VE) equal to 57.1% [99.5% CI: 14.7; 79.8]; significance was not retained on account of a lower CI limit below 20%) within 90 days after birth
  - reduction in significant severe RSV-LRTI cases on D90, 120, 150 and 180 (VE 81.8% [99.5% CI: 40.6; 96.3], 73.9% [97.58% CI: 40.6; 96.3], 70.9% [97.58% CI: 44.5; 85.9], 69.4% [97.58% CI: 44.3; 84.1] respectively)
  - reduction in hospital admissions, secondary endpoint: VE of 67.7% [99.17% CI: 15.9; 89.5] reported on D90 after birth before decreasing over time to values of 59.5% [99.17%: 8.3; 83.7], 56.4% [99.17% CI: 5.2; 81.5], 56.8% [99.17% CI: 10.1; 80.7], 33.3% [99.17% CI: -17.6; 62.9] on D120, 150, 180 and 360 after birth, respectively;
  - lack of robust data (primary endpoint) on the impact of vaccination on conventional hospitalisations and intensive care hospitalisations;
  - incomplete data on the vaccine efficacy of vaccination in premature newborns under 37 weeks of gestation;

– **The lack of correlate of protection** established for RSV infection prevention;

– **The immunogenicity data** in respect of the Abrysvo vaccine available to date for pregnant women, newborns and infants essentially obtained from intermediate analyses in the United States of the SAVVY Phase IIb study (406 pregnant women and 403 infants) demonstrating:
  - induction of higher RSV A and B neutralising antibody levels in women receiving vaccination with one of the candidate vaccines (RSVPreF) with different doses and formulations (including that of the Marketing Authorisation, MA) compared to the placebo group from 2 weeks post-vaccination and up to 6 months postpartum
  - similar antibody levels after vaccination at a dose of 120 µg (dose selected for the MA formulation) and 240 µg of RSVpreF
  - effective mother-to-child transplacental neutralising antibody transfer in umbilical cord and infant samples
  - similar neutralising antibody level obtained in umbilical cord blood regardless of the date of maternal vaccination between 24 and 36 weeks of gestation and neutralising antibody titre half-life for RSV A and B combined in infants varying from 39 to 40 days

– **The safety data** in respect of the Abrysvo vaccine assessed in over 4000 pregnant women and infants demonstrating:
  - a good safety profile with local reactions and systemic events occurring after administering RSVpreF vaccine most generally of slight to moderate severity
  - similar proportions of pregnant women presenting with severe adverse events (SAE) reported post-vaccination up to 6 months postpartum in RSVpreF and placebo groups (16.2% versus 15.2%). No AEs resulting in foetal or maternal death were assessed as being associated with maternal vaccination.
  - similar frequency of AEs and SAEs in participating infants reported in the RSVpreF and placebo groups
  - similar proportions of participating infants presenting with SAEs between birth and the age of 24 months in the RSVpreF group (17.5%) and in the placebo group (17.5%). In both groups, most of the SAEs reported on the date of data closure occurred between birth and 1 month of age (≤15.5%). Congenital abnormalities reported as SAEs occurred at a similar frequency in the RSVpreF and placebo groups (5.0% and 6.2%).
  - proportion of low-birth-weight infants reported at a similar frequency in the RSVpreF and placebo groups (5.1% and 4.3%).
  - a non-significantly higher proportion of premature births was reported in the RSVpreF group (5.7% [95% CI: 4.9; 6.5]) versus the placebo group (4.7% [95% CI: 4.1; 5.5]), corresponding to 201 premature infants in the RSVpreF group and 169 in the placebo group. The proportions of infants born prematurely according to the interval between vaccination and birth were calculated: when the interval between vaccination and birth was shorter (≤ 7 days), the proportion of premature newborns was of the same order of magnitude in the RSVpreF group and in the placebo group (5.5% versus 7.7% respectively). The occurrence of premature births was not considered by the primary investigator of the study to be correlated with vaccination and was not considered as an adverse effect of the vaccine. To

date, the European authorities have concluded that there is no signal of a potential risk of premature births.

– **The discontinuation of the Phase 3 clinical trial assessing the non-adjuvanted vaccine RSVPreF3-MAT** developed by the firm GSK and administered to pregnant women with a view to protecting newborns and infants against RSV, following the detection of a significant difference in premature births and deaths in infants whose mothers had been vaccinated with the candidate vaccine versus placebo: 238 premature births out of 3496 (6.8%) were reported in the vaccine arm and 86 out of 1739 (4.9%) in the placebo arm, representing approximately one additional premature birth per 54 vaccinated mothers. This significant difference was only observed in low- and middle-income countries and no significant difference was observed in high-income countries for premature births. The investigations on this vaccine are still ongoing and it is not yet possible at this stage to confirm or refute the role of the GSK non-adjuvanted RSVPreF3-MAT vaccine in these premature births or obtain an explanation of any mechanism;

– **The general principles of vaccinology suggest that the risk of interference between inactivated vaccines having a different antigenic content is probably limited**;

– **The immunogenicity data from co-administration** with other vaccines, which are limited to date:
  - with the diphtheria-tetanus-pertussis vaccine, dTCa: there were no safety problems when Abrysvo was administered at the same time as dTCa to healthy non-pregnant women. The immune responses to RSVA, RSVB, diphtheria and tetanus following co-administration were non-inferior to those after separate administration. However, the immune responses to the pertussis components were weaker following co-administration compared to separate administration and failed to meet the non-inferiority criterion. The clinical relevance of this observation is unknown.
  - with an influenza vaccine: no study assessing the safety and immune responses of RSV vaccines with influenza vaccines recommended for pregnant women. Data from a study conducted on adults aged over 65 years demonstrated numerically lower RSV A and B neutralisation titres and numerically lower influenza A and B virus haemagglutination inhibition titres following the concomitant administration of Abrysvo and inactivated seasonal influenza vaccine with adjuvant meeting non-inferiority criteria
  - with COVID-19 vaccines: no study assessing the safety and immune responses of RSV and COVID-19 vaccines has been identified to date.
  - with the vaccines administered to infants after birth: the lack of study of peripartum maternal vaccination interference on the immune response from DTCaPHibHB, pneumococcal and MenCC primary vaccination in infants.
  - In accordance with its MA, Abrysvo can be administered concomitantly with seasonal influenza vaccine. For the dTCa vaccine, a minimum two-week interval is recommended between administering this vaccine and Abrysvo.

– **The lack of post-marketing monitoring data in respect of this vaccine**;

– **The efficacy data in respect of Beyfortus and Synagis**: The efficacy of monoclonal antibodies in reducing RSV-related hospitalisations has been estimated at between 45% [95% CI: 23; 67] and 55% [95% CI: 38; 72] for Synagis (palivizumab) and between 62.1% [95% CI: -8.6; 86.8] and 83.2% [95%: 67.8; 92.0] for Beyfortus (nirsevimab). The data available to date do not allow robust comparisons with the Abrysvo vaccines (different populations included, different endpoints, etc.).

– **The cumulative real-line impact and efficacy data of Beyfortus since the first passive immunisation campaigns were launched for infants in several countries, confirming the efficacy of nirsevimab observed in clinical trials, even though they do not yet allow comparisons with maternal vaccination.** In France, a case-control study conducted by Santé Publique France demonstrated an efficacy of 75.9% [95% CI, 48.5; 88.7] of nirsevimab in preventing severe forms of RSV bronchiolitis. Another study modelled a significant impact of nirsevimab, estimating at around 5,800 (95% credibility interval, 3,700; 7,800) the number of RSV bronchiolitis hospitalisations prevented by administering nirsevimab during the 2023-24 season. International studies, in Spain and in the United States in particular, have also corroborated these findings, with efficacy rates varying depending on the contexts, age-groups and severity of the infection considered.

– **The lack of data to date relating to the risk of emergence of virus mutations** associated with the use of monoclonal antibodies, likely to lower the susceptibility of RSV to nirsevimab.

– **The international recommendations** published in recent months in different countries detailing their RSV vaccination strategy for pregnant women:
  - In the United States, the health authorities recommend the use of the Abrysvo vaccine between 32 and 36 weeks of gestation (versus between 24 and 36 weeks of gestation in the European MA). To justify the restriction of the vaccination window, the CDC reviewed the data available for women vaccinated between 32 and 36 weeks of gestation and considered the following items: i) the continued but reduced imbalance in premature births; ii) premature births in the vaccinated group occurring mostly at 36 weeks of gestation (72%, 49/68); iii) the reversal of the imbalance in premature births in the United States (the largest country taking part in the trial) from 4.0% in the vaccine group versus 4.4% in the placebo group.
  - in the United Kingdom, the *Joint Committee on Vaccination and Immunisation* (JCVI) recommends an annual vaccination programme for pregnant women and considers that it could be advantageous to decide to vaccinate from 28 weeks of gestation. No preference has been expressed for immunisation with Beyfortus or Abrysvo.
  - in Belgium, the Superior Health Council (SHC) recommends the use of Beyfortus or the Abrysvo vaccine, leaving the choice up to healthcare professionals and parents, and recommends a preferable period of 28 to 36 weeks of gestation for maternal vaccination.
  - in the Netherlands and Canada, passive immunisation of infants with monoclonal antibodies is recommended preferentially over maternal vaccination, in particular because it was considered that monoclonal antibodies make it possible to protect a greater number of infants, given that the protection provided by vaccination lasts for around 6 months and

therefore that vaccination is especially beneficial for women giving birth shortly before or during the RSV season.

- In Argentina, the Ministry of Health has approved the use of the Abrysvo vaccine between March and late September (autumn-spring) for pregnant women, between 32 and 36 weeks of gestation.
- A number of other countries have announced that they are working on drafting an RSV vaccination strategy (Ireland, Australia).

– **Acceptability data**:
  - acceptability surveys in respect of RSV vaccination conducted on pregnant women and healthcare professionals in France and internationally are encouraging. A study conducted in Saint Etienne describes a comparable proportion of pregnant women in favour de RSV vaccination to that observed for influenza, COVID-19 and whooping cough vaccination. Good knowledge of the illness, confidence in the vaccine, and promotion of vaccination by healthcare professionals providing antenatal care are also associated with superior acceptability of RSV vaccination by pregnant women. In a representative survey of the adult population living in France from the ICOVAC-France project, conducted between November and December 2023, 64% of French people were in favour of RSV vaccination for pregnant women (72% of men, versus only 57% of women).
  - the lack of relative acceptability data between passive immunisation with monoclonal antibodies and vaccination during pregnancy;

– **Vaccination coverage (VC) rates of recommended vaccines for pregnant women**:
  - the influenza VC for pregnant women between 2019 and 2021 was estimated at 21.1%;
  - the rate of pregnant women who had not received any COVID-19 vaccine before or during pregnancy was 25.4% in early March 2022;
  - the data for the VC rate of pertussis vaccines are not yet available in view of the recent vaccination recommendation for pregnant women (2022).

– **The medico-economic data** demonstrate that:
  - annual maternal vaccination was not cost-effective compared to no intervention.
  - annual maternal vaccination during pregnancy would be a cost-effective strategy compared to passive immunisation if the price per dose of vaccination during pregnancy was at least 50% lower than the price of monoclonal antibody.
  - superior cost-effectiveness of seasonal MV versus annual MV.
  - the predominance of seasonal passive immunisation programmes for infants over year-round passive immunisation.
  - combining an MV strategy with passive immunisation of high-risk infants, including those born prematurely or suffering from chronic illnesses, would make it possible to reduce the budgetary impact on the healthcare system compared to a programme only using Beyfortus.

– **The different possible scenarios for the period of vaccination** of pregnant women (annual vaccination to cover infants who will be between 0 and 6 months old during the epidemic period, vaccination from July to December to cover infants who will be up to 6

months old during the epidemic period, vaccination in pre-epidemic phase and until the end of the epidemic (from September to January for Metropolitan France) to facilitate communication and link up with the passive immunisation campaign)

– **The position of the members of the work group** regarding the RSV vaccination recommendation for pregnant women

– **The hearings of Prof. Marie-Anne Ramex-Welti, Head of the National Reference Centre for respiratory infection viruses, and Prof. Vassilis Tsatsaris, Head of Gynaecology-Obstetrics Department at Cochin Hospital Port Royal Maternity Department**, the minutes of which are featured in Appendices 4 and 5, respectively

– **The results of the public consultation**, organised from 29 March 2024 to 26 April 2024, targeting the main stakeholders in vaccination and presented in the form of an online questionnaire published in the HAS website. All the contributions received were analysed and taken into account with a view to drafting the final version of the document. All contributions received can be accessed on the HAS website.

After its assessment, the HAS recommends RSV vaccination for pregnant women in order to reduce the burden associated with RSV infections in infants. It deems that the Abrysvo vaccine can be used within the scope of this vaccination strategy. However, pending additional pharmacovigilance data and in order to limit the consequences in view of a potential excess risk of premature births (non-significant for this vaccine, but resulting in discontinued development of a competitor vaccine), and in view of the lack of vaccine efficacy data for premature newborns, the HAS recommends, as a precaution, that the vaccine be administered only between 32 and 36 weeks of gestation.

Furthermore, based on current knowledge, the HAS specifies that maternal vaccination and passive immunisation with monoclonal antibodies are two alternative strategies. The HAS recommends that both RSV infection prevention strategies be presented and explained to future parents during pregnancy to allow them to make an informed decision as to the protection of the infant, and deems that it is necessary to develop information materials tailored to future parents and the different healthcare professionals involved in this vaccination (general practitioners, midwives, paediatricians, pharmacists, gynaecologists-obstetricians, nurses, emergency physicians, resuscitation specialists). Nevertheless, in cases where pregnant women have not been vaccinated or where vaccination is probably not effective (premature newborns, interval of less than 14 days between vaccination and birth), the HAS advises boosting with passive immunisation with monoclonal antibodies. In the absence of efficacy and immunogenicity data for immunocompromised women, the HAS recommends preferentially administering monoclonal antibodies to the infant.

In view of the seasonal nature of RSV and efficacy data against severe forms demonstrating protection for the first six months postpartum, and in order to improve uptake and choice among families, the HAS recommends that the vaccination campaign be concomitant with the Beyfortus immunisation campaign, either before the start of the epidemic period and until the end of this period (from September to January for Metropolitan France). In order to optimise

involvement and acceptability among healthcare professionals and parents, the HAS recommends accessibility to both medicinal products (vaccine and monoclonal antibody) in maternity hospitals.

The HAS specifies that the Abrysvo vaccine can be administered at the same time as an influenza or COVID-19 vaccine and notes that, in accordance with its MA, a minimum interval of two weeks is recommended between administration of diphtheria-tetanus-acellular pertussis (dTCa) vaccine and administration of Abrysvo.

In the absence of data regarding the safety and efficacy of an additional dose of vaccine in the context of a successive pregnancy, the HAS has not delivered any opinion on the relevance of revaccination during subsequent pregnancies for a pregnant woman previously vaccinated during a prior pregnancy. Pending these data, and given the lowering of RSV neutralising antibody titres in pregnant women over time, the HAS recommends preferring passive immunisation of the newborn infant in the event of another pregnancy after a first vaccination.

The HAS notes the importance of control measures as complementary protective measures of maternal vaccination and passive immunisation of infants with monoclonal antibodies against RSV.

The HAS stresses the importance of setting up enhanced pharmacovigilance (post-approval safety studies) in particular with a view to documenting the potential risk of premature births.

This opinion may be reviewed with regard to the complete findings of ongoing trials, future trials, pharmacovigilance data and real-life data **from other countries.**